IB04/02190

सत्यमेव जयते

INTELLECTUAL PROPERTY INDIA

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Provisional Specification*** *filed in connection with Application for Patent No.* ***860/Del/2003*** *dated* ***1st July 2003.***

Witness my hand this 13th day of August 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

01 JUL 2003

C07H17/08

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"STABLE ORAL FORMULATIONS OF AZITHROMYCIN MONOHYDRATE"**

(b) that the Provisional Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. KAMAL MEHTA
b. RAJEEV SHANKER MATHUR
c. SUJATA PAUL
d. SANJEEV SETHI
e. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana). INDIA.

9. Following declaration was given by the inventors or applicants in the convention country:
We, KAMAL MEHTA, RAJEEV SHANKER MATHUR, SUJATA PAUL, SANJEEV SETHI, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representative.

a.

(KAMAL MEHTA)

b.

(RAJEEV SHANKER MATHUR)

c. Sujata Paul.

(SUJATA PAUL)

d.

(SANJEEV SETHI)

e.

(RAJIV MALIK)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
- a. Provisional Specification (3 copies)
- b. Drawings (3 copies)
- c. Priority document(s)
- d. Statement and Undertaking on FORM – 3
- e. Power of Authority (Not required)
- f. Fee Rs.3,000/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on

We request that a patent may be granted to us for the said invention.

Dated this **30TH** day of **June, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

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02 JUL 2003

FORM 2

01 JUL 2003

The Patents Act, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

STABLE ORAL FORMULATIONS OF AZITHROMYCIN MONOHYDRATE

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019
(A Company incorporated under the Companies Act, 1956)

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Azithromycin is the U.S.A.N. (generic name) for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A, a broad spectrum antimicrobial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. These patents disclose that azithromycin and certain derivatives thereof possess antibacterial properties and are accordingly useful as antibiotics. The stable oral formulations disclosed herein are useful for the treatment of various infections, like otitis media, respiratory infections of the bronchial tract, lungs, and sinus bacterial, opportunistic infections and other infections, which can be treated with said oral formulations.

WO03/018031 A2 discloses method of treating respiratory infections in human by administering a single dose of azithromycin. The invention therein is directed towards "single dose" of azithromycin which is administered only once over a 28 day period.

US5605889 discloses stable formulations of azithromycin dihydrate. The said patent teaches azithromycin formulations suitable for administration with food to prevention the food effect, said food effect being a major factor affecting bioavailability of azithromycin dosage form after oral administration.

WO01/00640 A1 discloses process for the production of stable azithromycin monohydrate. The patent specification therein teaches that "Azithromycin in the form of monohydrate is unstable since the crystal structure of azithromycin in the form of monohydrate may break down under normal humidity conditions within few hours". Azithromycin dihydrate is stable since under normal humidity conditions the crystal structure of dihydrate does not break down within few hours.

The embodiment disclosed in present specification uses azithromycin monohydrate which may be prepared by process according to WO01/00640 A1 patent specification or any other suitable method. The preferred method is as described in WO01/00640 A1 patent application.

It was observed that use of wet granulation or direct compression method produces formulations with problems of stability of azithromycin monohydrate in a sense that such formulations could not prevent conversion of azithromycin monohydrate to dihydrate or other hydrate forms. However, it

was surprisingly found that use of carefully selected excipients in suitable processing steps avoids this problem of conversion of azithromycin into hydrate forms other than monohydrate.

According to one embodiments of this specification the stable oral formulation of azithromycin monohydrate is disclosed. According to another embodiments of the specification the stable oral formulations of azithromycin base is disclosed. The formulations disclosed in various embodiments of the specification are stable and are expected to be bioequivalent to other formulations approved in various countries by respective regulatory authorities. The formulations of azithromycin monohydrate which are bioequivalent to those disclosed in the present specification are also considered to be within the scope of the appended claims. The suitable method for determining the conversion of azithromycin monohydrate to other hydrates is any method with substantial precision. The oral formulations disclosed in various embodiments of the specification are capable of preventing such a substantial conversion of monohydrate in to other hydrates thus producing stable oral formulations.

As described herein and in the appended claims the term "stable" refers to the oral formulations of azithromycin monohydrate which are substantially free from other hydrated forms such as dihydrate, trihydrate and such like. The term "formulations" refer to any oral dosage form such as tablet, capsule, suspension, oral powder for reconstitution, sachets, other unit dosage forms and such like. The tablet dosage forms may be prepared in various dosage forms for e.g. 250, 500 and 600 mg tablets. Other strengths may be prepared according to the type of infection to be treated and age and sex of the patient.

Following examples disclose various stable oral formulations of azithromycin monohydrate without limiting the scope of the present invention to particular formulations as disclosed. The other stable formulations of azithromycin monohydrate and azithromycin base are considered to be within the scope of the appended claims. The azithromycin monohydrate in following examples may be replaced with azithromycin base.

AZITHROMYCIN TABLETS 600/500/250 MG

Example 1

S.N	Ingredients	600 mg	500 mg	250 mg
Core Tablet				
Stage I				
	Azithromycin Monohydrate*	614.42	512.02	256.01
	Hydroxypropyl Cellulose	50	41.67	20.83
	Croscarmellose Sodium	60	50	25
	Sodium Lauryl Sulphate	1.8	1.5	0.75
Stage II				
	Pregelatinised Starch	64.8	54	27
	Dibasic Calcium Phosphate	196.41	163.67	81.83
	Microcrystalline cellulose	53.77	44.80	22.39
	Povidone K-30	20	16.67	8.33
Stage III				
	Magnesium Stearate	13	10.83	5.42
	Croscarmellose Sodium	55	45.83	22.92
	Sodium Lauryl Sulfate	1.8	1.5	0.75
	Colloidal Silicon Dioxide	13	10.83	5.42
	Talc	13	10.83	5.42
	Low substituted Hydroxypropyl Cellulose	15	12.5	6.25
	Microcrystalline cellulose	100	83.33	41.67
	Total	1272	1060	530
Coating (Stage IV)				
	Opadry	32	26.67	13.33
	Isopropyl Alcohol / Dichloromethane	q.s.	q.s.	q.s.

Process of preparation:

Core tablets:

Stage I:

1. Azithromycin Monohydrate, Hydroxypropyl Cellulose, Croscarmellose Sodium and Sodium Lauryl Sulphate were sifted through 30 mesh and mixed in a double cone blender.

2. The blend of step 1 was roller compacted and passed through the 22#.

Stage II:

3. Dibasic calcium Phosphate. Pregelatinised starch, Povidone K-30 and Microcrystalline Cellulose were sifted through 30# and mixed in a double cone blender.
4. The blend of step 3 was roller compacted and passed through 22#.

Stage III:

5. Talc, Colloidal Silicon dioxide, Croscarmellose sodium, Sodium lauryl sulfate, Low substituted hydroxypropyl cellulose and microcrystalline cellulose were sifted through 30# and mixed with material of Step 2 and step 4.
6. Magnesium Stearate was sifted through 44# and was added to the material of step 5 and was blended using double cone blender.
7. The material of step 6 was compressed to tablets using suitable tooling.

Coating:

8. Opadry was dispersed in the mixture of Isopropyl alcohol and methylene chloride to obtain a coating suspension.
9. Core tablets of step 7 were coated using the coating suspension of Step 8.

Example 2

S.N.	Ingredients	600 mg	500 mg	250 mg
Core Tablet				
	Azithromycin Monohydrate	614.42	512.02	256.01
	Pregelatinised Starch	64.8	54.0	27.0
	Dibasic Calcium Phosphate	263.18	219.32	109.66
	Croscarmellose Sodium	101.6	84.66	42.33
	Magnesium Stearate	10.8	9.0	4.5
	Sodium Lauryl Sulfate	3.6	3.0	1.5
	Colloidal Silicon Dioxide	10.8	9.0	4.5
	Talc	10.8	9.0	4.5
	Total	1080	900	450
Coating				
	Hydroxypropyl Methyl Cellulose	20	16.66	8.33
	Triacetin	2	1.66	0.83
	Talc	2.5	2.09	1.045
	Titanium Dioxide	2.5	2.09	1.045
	Isopropyl Alcohol / Dichloromethane	q.s.	q.s.	q.s.

Process of preparation:

Core tablets:

1. Azithromycin Monohydrate, Dibasic calcium Phosphate, Pregelatinised starch, part quantity of Croscarmellose sodium, Sodium lauryl sulfate and Magnesium Stearate were sifted through 30# and mixed in a double cone blender.
2. The blend of step 1 was roller compacted and passed through 18#.
3. Talc, Colloidal Silicon dioxide, remaining quantity of Croscarmellose sodium, Sodium lauryl sulfate and Magnesium Stearate were sifted through 30# and mixed with material of Step 2.
4. The material of step 3 was compressed using suitable tooling to obtain the tablets.

Coating:

5. Hydroxypropyl Methylcellulose, Triacetin, talc and Titanium dioxide were dispersed in purified water or mixture of Isopropyl alcohol and Dichloromethane to obtain a coating suspension .
6. The tablets of step 4 were coated using the coating suspension of Step 5.

Example 3

S.N.	Ingredients	600 mg	500 mg	250 mg
Core Tablet				
Stage 1				
	Azithromycin Monohydrate*	614.42	512.02	256.01
	Hydroxypropyl Cellulose	50	41.67	20.83
	Croscarmellose Sodium	60	50	25
	Sodium Lauryl Sulphate	1.8	1.5	0.75
Stage II				
	Pregelatinised Starch	64.8	54	27
	Dibasic Calcium Phosphate	171.41	142.84	71.42
	Microcrystalline cellulose	53.77	44.80	22.39
	Magnesium Hydroxide	25.0	20.83	10.42
	Povidone K-30	20	16.67	8.33
Stage III				
	Magnesium Stearate	13	10.83	5.42
	Croscarmellose Sodium	55	45.83	22.92
	Sodium Lauryl Sulfate	1.8	1.5	0.75
	Colloidal Silicon Dioxide	13	10.83	5.42
	Talc	13	10.83	5.42

	Low substituted Hydroxypropyl Cellulose	15	12.5	6.25
	Microcrystalline cellulose	100	83.33	41.67
	Total	1272	1060	530
Coating (Stage IV)				
	Opadry	32	26.67	13.33
	Isopropyl Alcohol / Dichloromethane	q.s.	q.s.	q.s.

Process of preparation:

Core tablets:

Stage I:

1. Azithromycin Monohydrate, Hydroxypropyl Cellulose, Croscarmellose Sodium and Sodium Lauryl Sulphate were sifted through 30 mesh and mixed in a double cone blender.
2. The blend of step 1 was roller compacted and passed through the 22#.

Stage II:

3. Dibasic calcium Phosphate, Magnesium hydroxide , Pregelatinised starch, Povidone K-30 and Microcrytalline Cellulose were sifted through 30# and mixed in a double cone blender.
4. The blend of step 3 was roller compacted and passed through 22#.

Stage III:

5. Talc, Colloidal Silicon dioxide, Croscarmellose sodium, Sodium lauryl sulfate, Low substituted hydroxypropyl cellulose and microcrystalline cellulose were sifted through 30# and mixed with material of Step 2 and step 4.
6. Magnesium Stearate was sifted through 44# and was added to the material of step 5 and was blended using double cone blender.
7. The material of step 6 was compressed to tablets using suitable tooling.

Coating:

8. Opadry was dispersed in the mixture of Isopropyl alcohol and methylene chloride to obtain a coating suspension .
9. Core tablets of step 7 were coated using the coating suspension of Step 8.

Example 4:

S.N.	Ingredients	Quantity/5ml
1.	Azithromycin Monohydrate	204.81 mg
2.	Sucrose	3660.19 mg
3.	Tribasic Sodium Phosphate (anhydrous)	20 mg
4.	Hydroxypropyl Cellulose - L	5 mg
5.	Colloidal Silicon Dioxide	6 mg
6.	Aspartame	20 mg
7.	Magnesium Hydroxide	80 mg
8.	Flavour	4 mg
	Total	4000 mg

Process of preparation:

1. The material of 1,3,4,5,6,7,8 and part quantity of Sucrose were sifted through 44 mesh and mixed for 10 minutes in double cone blender.
2. The remaining quantity of sucrose was sifted through 30 mesh and mixed with the blend of step 1 for 30 minutes in double cone blender.
3. The blend of step 2 was filled in HDPE bottles.

Example 5

Azithromycin Powder for Oral Suspension 100 mg/5ml and 200 mg/5ml

S.N.	Ingredients	200 mg/ 5ml	100 mg/ 5ml
	Compaction		
1	Azithromycin Monohydrate	208.808	102.404
2	Hydroxyproylcellulose – L (HPC-L)	25	12.5
3	Pregelatinised Starch	15	7.5

	Total	248.808	124.404
	Powder for Suspension		
4	Compacted Azithromycin	248.808	124.404
5	Sodium Alginate	23	23
6	Xanthan Gum	4	4
7	Sodium Hydroxide	6	6
8	Aspartame	16	16
9	Sodium Chloride	9	9
10	Flavour Cherry	7.5	7.5
11	Flavour Fruit gum	10	10
12	Colloidal Silicon Dioxide	8.5	8.5
13	Titanium Dioxide	3	3
14	FDC Red No. 40	1.3	1.3
15	Meglumine	2	2
16	Sucralose	20	10
17	Sucrose	3640.892	3775.296
	Total	4000	4000

Process of preparation:

Compaction

1. Azithromycin Monohydrate, hydroxypropylcellulose-L and Pregelatinized Starch were sifted through 30mesh and mixed for 20 min in double cone blender.
2. The blend was passed through roller compacter and 44-80 mesh fractions were collected. The fines were roll compacted.

Preparation of Blend for Suspension

3. Sodium Hydroxide was dissolved in purified water and part of sucrose was dissolved in purified water to obtain granulated sucrose.
4. The granulated Sucrose of step 3 was dried.
5. The material of 5 to 16 was sifted through 60mesh.
6. The compacted material of step 2 was mixed with material of step 5 to obtain a blend.
7. The blend of step 6 was filled in HDPE bottles.

Example 6

S.N.	Ingredients	200 mg/ 5ml	100 mg/ 5ml
	Compaction		
1	Azithromycin Monohydrate	208.808	102.404
2	Hydroxyproylcellulose – L (HPC-L)	25	12.5
3	Pregelatinised Starch	15	7.5
	Total	248.808	124.404
	Coating with Ethylcellulose		
4	Compacted Azithromycin	248.808	124.404
5	Ethylcellulose	20	10
6	Isopropyl Alcohol	q.s.	q.s.
7	Methylene Chloride	q.s.	q.s.
	Powder for Suspension		
8	Coated Azithromycin	268.808	134.404
9	Sodium Alginate	23	23
10	Xanthan Gum	4	4
11	Sodium Hydroxide	6	6
12	Aspartame	16	16
13	Sodium Chloride	9	9
14	Flavour Cherry	7.5	7.5
15	Flavour Fruit gum	10	10
16	Colloidal Silicon Dioxide	8.5	8.5
17	Titanium Dioxide	3	3
18	FDC Red No. 40	1.3	1.3
19	Meglumine	2	2
20	Sucralose	20	10
20	Sucrose	3620.892	3765.296
	Total	4000	4000

Process of preparation:

Compaction

1. Azithromycin Monohydrate, hydroxypropylcellulose-L and pregelatinised Starch was sifted through 30mesh and mixed for 20 min in double cone blender.
2. The blend of step 1 was passed through roller compacter and 44-80mesh fractions were collected. The fines were roller compacted.

Coating with Ethylcellulose

3. Ethylcellulose was dissolved in Isopropyl Alcohol and Methylene Chloride
4. The compacted material of step 2 was coated with ethylcellulose solution of step 3 using fluid bed processor.

Preparation of Blend for Suspension

5. Sodium Hydroxide was dissolved in purified water and part of sucrose was dissolved in purified water to obtain granulated sucrose.
6. The granulated Sucrose of step 3 was dried.
7. The material of 9 to 20 was passed through 60mesh.
8. The material of step 4 was mixed with material of step 7 to obtain the blend.
9. The blend of step 8 was filled in HDPE bottles.

Example 7

Azithromycin Powder for Oral Suspension 1 g Single dose packet

S.N.	Ingredients	1 g
	Compaction	
1	Azithromycin Monohydrate	1024.03
2	Hydroxyproylcellulose – L (HPC-L)	125
3	Pregelatinised Starch	30
	Total	1179.03
	Powder for Suspension	
4	Compacted Azithromycin	1179.03
5	Sodium Alginate	86
6	Xanthan Gum	20
7	Sodium Hydroxide	30
8	Aspartame	80
9	Sodium Chloride	45
10	Flavour Cherry	37.5
11	Flavour Fruit gum	50
13	Titanium Dioxide	15
14	FDC Red No. 40	6.5

15	Meglumine	10
16	Suralose	100
17	Sucrose	8340.97
	Total	10000

Process of preparation:

Compaction

1. Azithromycin Monohydrate, hydroxypropyl cellulose –L and pregelatinised Starch were passed through 30mesh and mixed for 20 min in double cone blender.
2. The blend of step 1 was passed through roller compactor and 44-80 mesh fractions were collected. The fines were roller compacted.

Preparation of Blend for Suspension

3. Sodium Hydroxide was dissolved in purified water and part of sucrose was dissolved in purified water to obtain granulated sucrose.
4. The granulated Sucrose of step 3 was dried.
5. The material of 5 to 17 was passed through 60mesh.
6. The material of step 2 was mixed with material of step 5 to obtain the blend.
7. The blend of step 6 was filled in HDPE bottles.

Example 8

S.N.	Ingredients	1 g
	Compaction	
1	Azithromycin Monohydrate	1024.03
2	Hydroxyproylcellulose – L (HPC-L)	125
3	Pregelatinised Starch	30
	Total	1179.03
	Coating with Ethylcellulose	
4	Compacted Azithromycin	1179.03
5	Ethylcellulose	100
6	Isopropyl Alcohol	q.s.
7	Methylene Chloride	q.s.

	Powder for Suspension	
8	Coated Azithromycin	1279.03
9	Sodium Alginate	86
10	Xanthan Gum	20
11	Sodium Hydroxide	30
12	Aspartame	80
13	Sodium Chloride	45
14	Flavour Cherry	37.5
15	Flavour Fruit gum	50
16	Titanium Dioxide	15
17	FDC Red No. 40	6.5
18	Meglumine	10
19	Sucralose	100
20	Sucrose	8240.97
	Total	4000

Process of preparation: The process of example 6 can be followed to prepare formulations of above example.

It would be appreciated by the person skilled in the art that the process as disclosed in various embodiments of the specification are not limited to specific example or specific make or machine as exemplified.

Dated **30TH** day of **June, 2003.**

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

The present invention relates to the stable oral formulations of azithromycin monohydrate or azithromycin base, process of its preparation and use of said formulations for the treatment of bacterial infections which can be treated with said formulations.